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REVIEW ARTICLE

Pharmacokinetics and Clinical Use of Incretin-Based Therapies in Patients with Chronic Kidney Disease and Type 2 Diabetes

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Abstract The prevalence of chronic kidney disease (CKD) of stages 3–5 (glomerular filtration rate [GFR] <60 mL/min) is about 25–30 % in patients with type 2 diabetes mellitus (T2DM). While most oral antidiabetic agents have limitations in patients with CKD, incretin-based therapies are increasingly used for the management of T2DM. This review analyses (1) the influence of CKD on the pharmacokinetics of dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists; and (2) the efficacy/safety profile of these agents in clinical practice when prescribed in patients with both T2DM and CKD. Most DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, alogliptin) are predominantly excreted by the kidneys. Thereby, pharmacokinetic studies showed that total exposure to the drug is increased in proportion to the decline of GFR, leading to recommendations for appropriate dose reductions according to the severity of CKD. In these conditions, clinical studies reported a good efficacy and safety profile in patients with CKD. In contrast, linagliptin is eliminated by a predominantly hepatobiliary route. As a pharmacokinetic study showed only minimal influence of decreased GFR on total exposure, no dose adjustment of linagliptin is required in the case of CKD. The experience with GLP-1 receptor agonists in patients with CKD is more limited. Exenatide is eliminated by renal mechanisms and should not be given in patients with severe CKD. Liraglutide is not eliminated by the kidney, but it should be used with caution because of the limited experience in patients with CKD. Only limited pharmacokinetic data are also available for lixisenatide, exenatide long-acting release (LAR) and other once-weekly GLP-1 receptor agonists in current development. Several case reports of acute renal failure have been described with GLP-1 receptor agonists, probably triggered by dehydration resulting from gastrointestinal adverse events. However, increasing GLP-1 may also exert favourable renal effects that could contribute to reducing the risk of diabetic nephropathy. In conclusion, the already large reassuring experience with DPP-4 inhibitors in patients with CKD offers new opportunities to the clinician, whereas more caution is required with GLP-1 receptor agonists because of the limited experience in this population.

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Key Points

An increasing number of patients with type 2 diabetes mellitus have impaired renal function, especially in the elderly population, but the use of glucose-lowering agents is challenging in these patients who require a dosing adjustment or have contraindications for safety reasons.

Although more recently available, dipeptidyl peptidase-4 inhibitors have been more carefully evaluated in patients with renal impairment than classical commonly prescribed glucose-lowering agents.

Dipeptidyl peptidase-4 inhibitors have been shown to be efficacious and safe in patients with renal impairment, but require dosing adjustment according to glomerular filtration rate decline (except for linagliptin).

The experience of glucagon-like peptide-1 receptor agonists in patients with renal impairment is more limited and thus caution is recommended and the drug should be stopped in the case of gastrointestinal adverse events with a risk of dehydration.

1 Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is rapidly increasing worldwide and the proportion of elderly people with T2DM is progressing in most countries. Numerous patients with T2DM have some degree of chronic kidney disease (CKD), which may be assessed by a reduction in estimated glomerular filtration rate (eGFR) and classified into various stages of CKD according to severity (from stage 1 to stage 5) [1, 2]. The presence of CKD may impact on the management of T2DM [3, 4]. A patient-centred approach is recommended in the management of hyperglycaemia of T2DM [5]. Among the various patient characteristics, renal function is a key variable to be taken into account when selecting the type and the daily dosage of glucose-lowering agents [6–8].

Kidney plays a major role in the clearance of drugs, in general [9], and of glucose-lowering agents used for T2DM, in particular [7]. Therefore, the management of glycaemia in patients with diabetes and CKD is quite challenging [10] and the questions of which hypoglycaemic agents to use in T2DM subjects with CKD and how to use them are of major practical importance [11]. The presence of CKD may deeply impact the pharmacokinetics and thereby should influence choices, dosing and monitoring of hypoglycaemic agents according to the reduction of GFR [10, 12, 13].

Incretin-based therapies include either oral agents acting as inhibitors of dipeptidyl peptidase-4 (DPP-4), also known as gliptins, or injectable agents acting as agonists of glucagon-like peptide-1 (GLP-1) receptors [14]. By inhibiting the inactivation of both endogenous GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), DPP-4 inhibitors stimulate insulin secretion and reduce glucagon secretion, both in a glucose-dependent manner. This dual effect results in a clinically relevant improvement of glucose control without inducing hypoglycaemia or weight gain in T2DM patients [15]. Subcutaneous injection of GLP-1 receptor agonists exerts a more marked reduction in hyperglycaemia, together with significant weight loss resulting from increased satiety due to delayed gastric emptying and central anorectic activity by GLP-1 [16, 17].

Although dedicated studies in T2DM patients with CKD are scarce or of rather poor quality with commonly used glucose-lowering agents (metformin, sulphonylureas, glinides, thiazolidinediones) [18], new incretin-based medications have been much better evaluated from a pharmacokinetic and clinical point of view in patients with CKD [19–22].

The present review aims at providing an updated analysis of the pharmacokinetic characteristics of incretin-based therapies, both DPP-4 inhibitors and GLP-1 receptor agonists, in patients with various degrees of CKD. In addition, the reported clinical experience in diabetic patients with CKD and the renal safety of these two pharmacological classes targeting the incretin system will also be briefly summarized. This piece of information should help the physician to decide how to use incretin-based therapies in patients with CKD.

2 Literature Search

To identify relevant studies in this review, an extensive literature search of Medline (based on titles and abstracts) was performed from January 2005 to 1 July 2014, with the MESH terms of DPP-4 inhibitors or GLP-1 receptor agonists combined with any of the following terms: ‘chronic kidney disease’, ‘renal impairment’ or ‘renal insufficiency’. Each generic name—sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin for the DPP-4 inhibitors; exenatide, liraglutide, lixisenatide for the GLP-1 receptor agonists—was also combined with each of the various terms corresponding to CKD. No language restrictions were imposed. No a priori specific inclusion or exclusion criteria were imposed during the literature search. Reference lists of original studies, narrative reviews and

previous systematic reviews were also carefully examined. However, because this article is a narrative review rather than a systematic review, no detailed information is provided regarding the study flow and the assessment of the quality of the evidence. The lack of a systematic approach may be considered as a limitation of this review and the recommendations made.

3 Relationships Between Incretin Hormones and Kidneys

Both GLP-1 receptors and DPP-4 enzyme are expressed in the kidney in various species [23]. Although renal GLP-1 receptors have been identified, their exact localization and physiological role are incompletely understood. Activation of GLP-1 receptors in the kidney leads to diuretic and natriuretic effects, possibly through direct actions on renal tubular cells and sodium transporters, especially the inhibition of the sodium-hydrogen ion exchanger isoform 3 in the proximal tubule [24]. This may in part explain why GLP-1 receptor agonists have antihypertensive effects. GFR is regulated by GLP-1, but the mechanisms are complex and may depend on glycaemic conditions. Atrial natriuretic peptide or the renin–angiotensin system may be involved in the signalling of GLP-1-mediated renal actions [24].

Several studies in rodents have shown that GLP-1 therapy is renoprotective beyond metabolic improvements in models of diabetic nephropathy and acute kidney injury [24, 25]. Incretin-based therapy reduces albuminuria, glomerulosclerosis, oxidative stress, inflammation and fibrosis in the kidney, partially through GLP-1 receptor-independent pathways [23]. GLP-1 has a crucial role in protection against increased renal oxidative stress under chronic hyperglycaemia, by inhibition of NAD(P)H oxidase, a major source of superoxide, and by cAMP-PKA pathway activation [26]. Additionally, there is evidence that GLP-1 receptor agonists influence the water and electrolyte balance. These effects may represent new ways to improve or even prevent diabetic nephropathy [26, 27].

Experimental data in humans underlined the importance of the kidneys for the final elimination of both GIP and GLP-1. The initial DPP-4-mediated degradation of both hormones was almost unaffected by impairments in renal function. Delayed elimination of GLP-1 and GIP in renal impairment may influence the pharmacokinetics and pharmacodynamics of DPP-4-resistant incretin derivatives to be used for the treatment of patients with T2DM [28]. In a more recent study, and unexpectedly, degradation and elimination of the intact and metabolite forms of GLP-1 and GIP appeared preserved, although reduced, in patients with haemodialysis-dependent kidney failure [29]. Because the kidney plays an important role in the excretion of incretin metabolites and most GLP-1 receptor agonists and DPP-4 inhibitors, special attention is required when applying incretin-based therapy in patients with CKD [23].

4 DPP-4 Inhibitors

Several DPP-4 inhibitors (gliptins) are already available and other are in clinical development [15, 30]. They are characterized by different pharmacokinetic properties [31, 32]. DPP-4 inhibitors have been particularly well studied in patients with CKD [19–22]. Sitagliptin [33], vildagliptin [34, 35], saxagliptin [36] and alogliptin [37] (data only available as abstract, but complementary information available in the European Medicines Agency [EMA] assessment report [38] and in the US Food and Drug Administration [FDA] report [39]) are largely excreted by the kidneys. In contrast, linagliptin is mainly excreted by the biliary route rather than by the kidney (<5 %) [40, 41]. In all studies involving DPP-4 inhibitors, the following populations have been tested: normal kidney function, creatinine clearance (CL_{CR}) >80 mL/min; mild CKD, CL_{CR} 51–80 mL/min; moderate CKD, CL_{CR} 31–50 mL/min; severe CKD, CL_{CR} ≤30 mL/min; end-stage renal disease (ESRD), CL_{CR} ≤30 mL/min undergoing haemodialysis.

4.1 Sitagliptin

4.1.1 Pharmacokinetics

The pharmacokinetic properties of sitagliptin have been previously reviewed [31, 32, 42]. Metabolism is a minor elimination pathway of sitagliptin, as almost 80 % of an administered dose is eliminated unchanged in the urine [42]. The pharmacokinetics of single doses of sitagliptin 50 mg were evaluated in patients with various degrees of CKD: mild, moderate, severe, ESRD on haemodialysis, and normal renal function used as reference [33]. Increases in sitagliptin exposure assessed by area under plasma concentration–time curve (AUC) from time zero to infinity (AUC_{∞}) were ~1.6-fold, ~2.3-fold, ~3.8-fold and ~4.5-fold higher for patients with mild CKD, moderate CKD, severe CKD and ESRD, respectively, as compared with levels obtained in subjects with normal renal function (Table 1). Similarly, mean maximum plasma concentration (C_{max}) progressively increased, although by a lower rate than did AUC_{∞}, according to the reduction in GFR, whereas median time to reach C_{max} (t_{max}) was almost unaffected. Elimination half-life ($t_{½}$) of sitagliptin progressively increased while corresponding renal clearance (CL_R) progressively decreased according to the reduction of CL_{CR} (Table 1). Based on these findings, sitagliptin dose

Table 1 Key pharmacokinetic parameters of dipeptidyl peptidase-4 (DPP-4) inhibitors in subjects with various degrees of chronic kidney disease (CKD; according to the level of creatinine clearance) compared with subjects with normal renal function (no CKD). Results are expressed as mean data ± standard deviation ([a]) or mean data with [% coefficient of variation] ([b]), except for time to reach maximum concentration (t_{max}; median, range)

Drug and parameter	Dosing reference	No CKD	Mild CKD	Moderate CKD	Severe CKD	Haemodialysis
Sitagliptin	Single-dose	Pooled (58–151)	$N = 6$	$N = 6$	$N = 6$	$N = 6$
AUC_{∞} (μmol·h/L)	50 mg	4.40 (NA)	7.09 (NA)	9.96 (NA)	16.6 (NA)	19.8 (NA)
GMR (90 % CI)	Bergman et al. [33]		1.61 (1.43–1.81)	2.26 (2.02–2.53)	3.77 (3.37–4.22)	4.50 (4.03–5.03)
C_{max} (nmol/L)		391 (NA)	527 (NA)	560 (NA)	684 (NA)	556 (NA)
GMR (90 % CI)			1.35 (1.15–1.58)	1.43 (1.23–1.67)	1.75 (1.51–2.03)	1.42 (1.22–1.65)
t_{max} (h; median, range)		3.0 (NA)	3.0 (NA)	3.0 (NA)	3.5 (NA)	5.0 (NA)
$t_{½}$ (h)		13.1 (NA)	16.1 (NA)	19.1 (NA)	22.5 (NA)	28.4 (NA)
CL_R (mL/min)		339 (NA)	242 (NA)	126 (NA)	60 (NA)	NA
Vildagliptin	Multiple-dose	Pooled $N = 46$	$N = 16$	$N = 16$	$N = 16$	$N = 16$
AUC_{τ} (ng·h/mL)	50 mg/day for 14 days	990 ± 237[a]	1,323 ± 291[a]	1,810 ± 688[a]	2,113 ± 1,130[a]	NA
GMR (90 % CI)	He et al. [34, 35]		1.40 (1.24–1.57)	1.71 (1.52–1.93)	2.00 (1.77–2.26)	NA
C_{max} (ng/mL)		251 ± 79[a]	326 ± 77[a]	343 ± 139[a]	361 ± 137[a]	NA
GMR (90 % CI)			1.37 (1.17–1.60)	1.32 (1.12–1.55)	1.36 (1.15–1.61)	NA
t_{max} (h; median, range)		1.5 (0.5–3.0)	1.5 (0.5–2.0)	2.0 (0.5–3.0)	1.8 (1.0–3.0)	NA
$t_{½}$ (h)		2.8 ± 2.1[a]	2.7 ± 1.2[a]	3.1 ± 1.0[a]	3.6 ± 1.3[a]	NA
CL_R (mL/min)		167 (NA)	112 (NA)	62 (NA)	27 (NA)	NA
Saxagliptin	Single-dose	$N = 8$	$N = 8$	$N = 8$	$N = 7$	$N = 8$
AUC_{∞} (ng·h/mL)	10 mg	215 [25][b]	249 [36][b]	303 [35][b]	434 [40][b]	170 [37][b]
GMR (90 % CI)	Boulton et al. [36][c]		1.16 (NA)	1.41 (NA)	2.08 (NA)	NA[d]
C_{max} (ng/mL)		54 [25][b]	75 [26][b]	58 [36][b]	72 [38][b]	46 [35][b]
GMR (90 % CI)			NA	NA	NA	NA
t_{max} (h; median, range)		0.63 (0.50–1.50)	0.88 (0.25–1.50)	1.50 (0.50–5.00)	1.00 (0.50–1.00)	0.88 (0.50–3.00)
$t_{½}$ (h)		3.09 ± 0.65[a]	3.50 ± 1.62[a]	4.02 ± 1.23[a]	4.41 ± 1.14[a]	3.39 ± 0.21[a]
CL_R (mL/min)		153 ± 23[a]	131 ± 37[a]	61 ± 28[a]	25 ± 9[a]	NA
5-hydroxy-saxagliptin		$N = 8$	$N = 8$	$N = 8$	$N = 7$	$N = 8$
AUC_{∞} (ng·h/mL)		569 [18][b]	950 [30][b]	1,660 [50][b]	2,574 [26][b]	2,330 [30][b]
GMR (90 % CI)			1.67 (NA)	2.92 (NA)	4.47 (NA)	NA
C_{max} (ng/mL)		92 [32][b]	129 [26][b]	135 [35][b]	131 [34][b]	125 [37][b]
GMR (90 % CI)			NA	NA	NA	NA
t_{max} (h; median, range)		1.25 (0.92–2.00)	1.75 (1.00–8.00)	4.00 (2.00–8.28)	5.00 (2.00–8.00)	2.63 (2.00–4.00)
$t_{½}$ (h)		3.85 ± 0.56[a]	5.83 ± 2.72[a]	8.55 ± 2.44[a]	9.88 ± 1.28[a]	12.51 ± 1.84[a]
CL_R (mL/min)		76 ± 11[a]	52 ± 17[a]	28 ± 13[a]	12 ± 3[a]	NA

Table 1 continued

Drug and parameter	Dosing reference	No CKD	Mild CKD	Moderate CKD	Severe CKD	Haemodialysis
Alogliptin	Single-dose	$N = 6$	$N = 6$			
AUC_{∞} (ng·h/mL)	25 mg	3,261.24 [10][b]	5,738.80 [39][b]			
GMR (90 % CI)	Karim et al. [37], EPAR [38], FDA report [39]		1.71 (1.35–2.17)	2.12 (NA)	3.51 (NA)	4.77 (NA)
C_{max} (ng/mL)		285.83 [29][b]	327.50 [26][b]			
GMR (90 % CI)			1.13 (NA)	1.42 (NA)	1.27 (NA)	1.32 (NA)
t_{max} (h; median)		1.475 [120][b]	1.667 [75][b]			
$t_{½}$ (h)		27.89 [14][b]	40.41 [12][b]			
CL_R (mL/min)		NA	NA			
Linagliptin	Single-dose	$N = 6$	$N = 6$	$N = 6$	$N = 6$	$N = 6$
$AUC_{0–24}$ (nmol·h/L)	5 mg	101 [32.6][b]	130 [11.0][b]	158 [44.3][b]	142 [26.3][b]	155 [16.8][b]
GMR (90 % CI)	Graefe-Mody et al. [41]		1.29 (1.01–1.66)	1.56 (1.06–2.32)	1.41 (1.04–1.91)	1.54 (1.18–2.00)
C_{max} (nmol/L)		7.32 [62.7][b]	9.20 [18.1][b]	11.5 [89.1][b]	10.8 [55.0][b]	11.0 [28.6][b]
GMR (90 % CI)			1.26 (0.80–1.96)	1.57 (0.77–3.19)	1.47 (0.83–2.61)	1.50 (0.94–2.41)
t_{max} (h; median, range)		2.25 (0.50–8.00)	1.50 (0.50–3.03)	2.25 (0.75–4.00)	1.50 (0.75–3.00)	3.00 (1.00–4.00)
$t_{½}$ (h)		NA	NA	NA	133 ± 51.0	129 ± 21.7
$CL_{R0–24}$ (mL/min)		4.06 [119][b]	4.50 [132][b]	4.12 [208][b]	3.83 [55.0][b]	
Linagliptin	Multiple-dose	$N = 6$	$N = 6$	$N = 6$		
$AUC_{\tau,ss}$ (nmol·h/L)	5 mg/day for 7 days	154 [21.2][b]	166 [10.3][b]	263 [25.6][b]		
GMR (90 % CI)	Graefe-Mody et al. [41]		1.08 (0.91–1.28)	1.71 (1.34–2.18)		
$C_{max,ss}$ (nmol/L)		13.2 [38.9][b]	12.9 [24.5][b]	19.3 [41.3][b]		
GMR (90 % CI)			0.98 (0.70–1.39)	1.46 (0.98–2.19)		
$t_{max,ss}$ (h; median, range)		0.52 (0.50–1.50)	2.50 (0.533–3.10)	1.27 (0.75–3.00)		
$t_{½,ss}$ (h)		192 [31.4][b]	233 [17.6][b]	190 [32.5][b]		
$CL_{R0–24,ss}$ (mL/min)		48.9 [40.3][b]	39.4 [38.6][b]	27.1 [24.2][b]		

Table 1 continued

Drug and parameter	Dosing reference	No CKD	Mild CKD	Moderate CKD	Severe CKD	Haemodialysis
Gemigliptin	Single-dose	$N = 6/6/5/6$	$N = 6$	$N = 6$	$N = 6$	$N = 6$
AUC_{∞} (ng·h/mL)	100 mg	1,963 ± 481[a]	2,305 ± 175[a]	3,425 ± 795[a]	3,070 ± 692[a]	3,262 ± 795[a]
	Shon et al. [85]	1,667 ± 298[a]				
		2,066 ± 642[a]				
		1,947 ± 550[a]				
GMR (90 % CI)			1.20 (0.97–1.49)	2.04 (1.62–2.55)	1.50 (1.13–2.01)	1.69 (1.30–2.19)
C_{max} (ng/mL)		183 ± 64[a]	194 ± 43[a]	248 ± 57[a]	211 ± 67[a]	173 ± 44[a]
		171 ± 56[a]				
		182 ± 91[a]				
		141 ± 43[a]				
GMR (90 % CI)			1.10 (0.80–1.50)	1.49 (1.10–2.02)	1.22 (0.74–1.99)	1.25 (0.92–1.70)
t_{max} (h; median, range)		1.0 (1.0–6.0)	1.0 (0.5–3.0)	1.0 (0.5–2.0)	1.0 (1.0–6.0)	3.0 (2.0–4.0)
		1.5 (0.5–2.0)				
		2.0 (1.0–2.0)				
		1.5 (1.0–4.0)				
$t_{½}$ (h)		18.9 ± 2.1[a]	18.9 ± 4.2[a]	23.3 ± 5.7[a]	21.3 ± 4.9[a]	17.8 ± 3.91[a]
		15.1 ± 2.7[a]				
		18.8 ± 1.1[a]				
		18.7 ± 1.4[a]				
CL_R (mL/min)		273 ± 144[a]	348 ± 156[a]	79 ± 43[a]	42 ± 27[a]	NA
		272 ± 97[a]				
		314 ± 109[a]				
		321 ± 112[a]				

AUC area under plasma concentration–time curve, AUC_{τ} AUC during dosage interval, $AUC_{\tau,ss}$ AUC_{τ} at steady state, AUC_{0-24} AUC from 0 to 24 h, AUC_{∞} AUC from time zero to infinity, *CI* confidence interval, CL_R renal clearance, CL_{R0-24} CL_R from 0 to 24 h, $CL_{R0-24,ss}$ CL_{R0-24} at steady state, C_{max} maximum plasma concentration, $C_{max,ss}$ C_{max} at steady state, *EPAR* European Public Assessment Report, *FDA* US Food and Drug Administration, *GMR* geometric mean ratio between renal impairment and normal kidney function, *NA* not available, $t_{½}$ terminal plasma half-life, $t_{½,ss}$ $t_{½}$ at steady state, $t_{max,ss}$ t_{max} at steady state

[c] Model-derived point estimates for the midpoint of each renal impairment category

[d] NA without post-dose haemodialysis

adjustments are recommended for patients with moderate CKD (50 mg daily) or severe CKD or ESRD (25 mg daily) to provide plasma sitagliptin exposure comparable to that of patients with normal renal function (100 mg daily).

4.1.2 Clinical Use

Sitagliptin was generally well tolerated and provided effective glycaemic control in patients with T2DM and moderate to severe CKD, including patients with ESRD on haemodialysis [43, 44]. In patients with T2DM and moderate to severe CKD, sitagliptin (50–25 mg/day, respectively) and glipizide provided similar reduction in glycated haemoglobin (HbA_{1c}). Sitagliptin was generally well tolerated, with a lower risk of hypoglycaemia (6.2 versus 17.0 %) and weight loss (−0.6 kg) versus weight gain (+1.2 kg), relative to glipizide [45]. A general equation has been proposed to rapidly calculate the specific time of effect duration for the different dose schedules in the case of CKD [46].

In patients with T2DM and ESRD on haemodialysis therapy, sitagliptin 25 mg/day was almost as effective in reducing HbA_{1c} as glipizide (nonsignificant difference of 0.15 % after 54 weeks), with a lower incidence of symptomatic hypoglycaemia (6.3 versus 10.8 %) and severe hypoglycaemia (0 versus 7.7 %) [47]. Thus, sitagliptin may be considered as another option for managing T2DM in ESRD patients treated by haemodialysis [48].

New-onset diabetes after transplantation is a serious complication after kidney transplantation, but therapeutic strategies remain underexplored. In these patients as in common T2DM subjects, sitagliptin increases insulin secretion and reduces fasting and postprandial plasma glucose. The treatment was well tolerated, and sitagliptin seems safe in this population [49, 50].

Current evidence suggests that there is no need for active monitoring of potential renal toxicity of sitagliptin [42, 51].

4.2 Vildagliptin

4.2.1 Pharmacokinetics

Vildagliptin is primarily metabolized via hydrolysis and the metabolites are predominantly excreted by the kidneys. Unchanged drug and a carboxylic acid inactive metabolite (LAY151) were the major circulating components in plasma, accounting for 25.7 % (parent drug vildagliptin) and 55 % (LAY151) of total plasma radioactivity AUC. To a smaller extent, vildagliptin is also excreted by the kidneys as the unchanged drug (23 % after an oral dose) [52]. Therefore, CKD may somewhat alter the pharmacokinetics of vildagliptin [34]. In a dedicated study where each subject received vildagliptin 50 mg dosed orally once daily for 14 days, the mean AUC of vildagliptin after 14 days in patients with mild, moderate and severe CKD increased by 40, 71 and 100 %, respectively, and the C_{max} of vildagliptin showed similar and minimal increases of 37, 32 and 36 %, respectively, compared with matched subjects with normal renal function (Table 1) [35]. The exposure (AUC and C_{max}) to the metabolite LAY151 increased even more importantly according to GFR decline (data not shown); as this metabolite is inactive, the clinical significance of such an increase is most probably trivial. CL_R of vildagliptin in healthy volunteers averaged about 10 L/h, and decreased in subjects with varying degrees of renal impairment with a significant correlation with the reduction in GFR ($r^2 = 0.75$). However, the total exposure (AUC) to vildagliptin did not show a clear correlation with the severity of CKD assessed by decreased GFR. Vildagliptin was removed by haemodialysis to a limited extent (3 %) [35] The lack of a clear correlation between the increased exposure to vildagliptin and the severity of CKD may indicate that the kidneys contribute not only to the excretion but also, and predominantly, to the hydrolysis metabolism of vildagliptin. From a pharmacokinetic perspective, the approximate 2-fold increase in exposure suggests that the dose of vildagliptin for patients with moderate CKD (eGFR $\geq$30 to $\leq$50 mL/min) and severe CKD (eGFR $<$ 30 mL/min) should be reduced to half of the daily dose for patients with normal renal function (50 mg once daily instead of 50 mg twice daily) [34, 53]. Because vildagliptin is a substrate for the DPP-4 catalytic site with a slow dissociation rate (rather than a competitive inhibitor), the drug maintains essentially complete inhibition of DPP-4 for a longer period following oral administration than that predicted by a apparent short half-life (which is, however, significantly increased in the presence of CKD) [54]. These pharmacological properties explain why the dose of 50 mg vildagliptin can be given once a day rather than split into 25 mg twice a day in patients with CKD.

4.2.2 Clinical Use

In a 24-week study of 515 patients with T2DM and moderate or severe CKD, vildagliptin (50 mg once daily) added to ongoing antidiabetic therapy had a safety profile similar to placebo and elicited a statistically and clinically significant decrease in HbA_{1c} [55]. These results were confirmed after a 1-year observation [56]. HbA_{1c} reductions seen in T2DM patients with CKD treated with 50 mg once daily were similar to the reductions observed with the vildagliptin 50 mg twice-daily dose in a similar population with preserved renal function and a similar baseline HbA_{1c} [55]. In another study, the safety profile of vildagliptin

50 mg as an add-on to metformin was similar in patients with mild CKD and normal renal function [57]. In a pooled analysis of 38 studies where vildagliptin was given for 12–104 weeks in patients with T2DM, the presence of mild CKD did not adversely affect the safety of vildagliptin relative to patients with normal renal function [58]. Available results support a favourable efficacy, safety and tolerability profile for vildagliptin in T2DM with moderate or severe renal impairment providing that the daily dose is reduced by half [53]. Vildagliptin 50 mg once daily was also effective and safe as a treatment for diabetic patients undergoing haemodialysis [59, 60] or peritoneal dialysis [60] as well as in patients with severe CKD and long-standing T2DM not adequately controlled with insulin therapy [61]. Finally, treatment with vildagliptin 50 mg once daily in kidney transplant recipients with new-onset diabetes after transplantation was safe and efficient in placebo-controlled trials, providing a novel treatment alternative for this specific form of diabetes [62, 63].

4.3 Saxagliptin

4.3.1 Pharmacokinetics

Saxagliptin is metabolized in vivo to form an active metabolite, 5-hydroxy-saxagliptin. This main metabolite of saxagliptin also exerts a significant DPP-4 inhibition and is half as potent as the parent compound. Both parent drug and metabolite are excreted primarily via the kidneys [31, 32, 64]. The pharmacokinetics of saxagliptin and its pharmacologically active metabolite were compared in nondiabetic subjects with normal renal function, in patients with mild, moderate and severe CKD, and in those with ESRD [36]. All subjects received a single oral dose of saxagliptin 10 mg. Using a model-based approach and in comparison with healthy subjects, the geometric mean AUC_{∞} for saxagliptin was 16, 41 and 108 % higher in subjects with mild, moderate or severe CKD, respectively. AUC_{∞} values for 5-hydroxy-saxagliptin were 67, 192 and 347 % higher in subjects with mild, moderate or severe CKD, respectively (Table 1). Elimination $t_{½}$ of saxagliptin and 5-hydroxy-saxagliptin progressively increased while corresponding CL_R progressively decreased according to the reduction of CL_{CR}. Consequently, one half the usual dose of saxagliptin 5 mg (i.e. 2.5 mg orally once daily) is recommended for patients with moderate or severe CKD or ESRD on haemodialysis, but no dose adjustment is recommended for those with mild CKD. Using exposure modelling of saxagliptin and its active metabolite, 5-hydroxy-saxagliptin, a pharmacometric approach was developed to quantify the impact of chronic CKD and haemodialysis on systemic drug exposure [65].

4.3.2 Clinical Use

A 12-week study evaluated the efficacy and safety of saxagliptin 2.5 mg versus placebo in patients with T2DM and CKD (CL_{CR} <50 mL/min) [66]. Oral glucose-lowering agents and insulin therapy present at enrolment were continued throughout the study. Adjusted mean HbA_{1c} decreases from baseline to week 12 were numerically greater with saxagliptin than with placebo in the subgroups of patients with moderate CKD (≥30 CL_{CR} <50 mL/min) and severe CKD (CL_{CR} <30 mL/min), but not in ESRD patients on haemodialysis. After an extended follow-up of 52 weeks, the adjusted mean decrease in HbA_{1c} was greater with saxagliptin than placebo (difference, −0.73 %, $p < 0.001$). Again, reductions in HbA_{1c} were numerically greater with saxagliptin 2.5 mg than placebo in patients with CKD rated as moderate or severe, but similar to placebo for those with ESRD on haemodialysis. Saxagliptin was generally well tolerated, with similar proportions of patients reporting hypoglycaemic events as in the placebo group. Thus, saxagliptin 2.5 mg once daily offers sustained efficacy and good tolerability for patients with T2DM and moderate to severe CKD, but should not be recommended in patients with ESRD [67].

In the large prospective SAVOR-TIMI 53 cardiovascular outcomes trial [68], the incidence of a secondary composite renal end point (doubling of creatinine level, initiation of haemodialysis, renal transplantation, or creatinine >6.0 mg/dL [530 μmol/L]) was similar in the saxagliptin group and in the placebo group after a median follow-up of 2.1 years: 194/8,280 (2.2 %) versus 178/8,212 (2.0 %), odds ratio 1.08 (95 % confidence interval [CI] 0.88–1.32); $p = 0.46$. However, a significant between-group difference was observed regarding the changes in microalbuminuria, with more patients showing improvement (10.7 versus 8.7 %) and fewer patients exhibiting deterioration (13.3 versus 15.9 %) in the saxagliptin group as compared with the placebo group ($p < 0.001$).

4.4 Alogliptin

4.4.1 Pharmacokinetics

Alogliptin is rapidly absorbed and eliminated slowly, primarily via urinary excretion [31, 32, 69]. The results of a single-dose (50 mg) pharmacokinetic study in patients with CKD showed an increase in alogliptin total exposure compared with healthy volunteers: approximately 1.7-, 2.1-, 3.5- and 4.8-fold increases in patients with mild CKD, moderate CKD, severe CKD and ESRD, respectively (Table 1) [37]. Based on these findings, to achieve plasma alogliptin concentrations comparable to those in patients with normal renal function, alogliptin dose adjustments are

recommended for patients with T2DM and moderate to severe CKD, including those with ESRD requiring haemodialysis (respectively, 12.5 mg or 6.25 mg instead of 25 mg once daily) [38, 39].

4.4.2 Clinical Use

A small, 6-month, open-label study in T2DM patients with CKD reported safe use of alogliptin but no detectable favourable effects on renal function [70]. In patients with CKD caused by immunological abnormalities and treated with steroids, alogliptin improved steroid-induced hyperglycaemia by decrease of glucagon levels through an increase in plasma GLP-1 levels [71].

Alogliptin 6.25 mg/day as monotherapy or in combination with other oral antidiabetic agents improved glycaemic control and was generally well tolerated in patients with haemodialysis over a 48-week period [72]. These results were confirmed in a longer term (2-year) study with alogliptin monotherapy, suggesting its efficacy as a new treatment strategy in diabetic patients with ESRD treated by haemodialysis [73].

In the EXAMINE cardiovascular outcomes trial in patients with T2DM and a recent acute coronary syndrome, changes in estimated GFR according to baseline kidney function and incidences of initiation of haemodialysis were similar in the alogliptin group and in the placebo group (0.9 versus 0.8 %) [74]. The effect of alogliptin on microalbuminuria has not been reported in this study.

4.5 Linagliptin

4.5.1 Pharmacokinetics

In contrast to the previously described DPP-4 inhibitors, which are mostly excreted unchanged in the urine, linagliptin is predominantly eliminated by a hepatobiliary route [31, 32, 75]. Therefore, it can be used in all stages of CKD without dose adjustments [76]. The influence of various degrees of CKD on the exposure of linagliptin was assessed in subjects with and without T2DM [41]. Linagliptin pharmacokinetics (5 mg once daily) were studied under single-dose and steady-state conditions (administration for 7–10 days) in subjects with mild, moderate, and severe CKD and ESRD on haemodialysis, and compared with the pharmacokinetics in subjects with normal renal function. Renal excretion of unchanged linagliptin was <7 % in all groups. Although there was a tendency towards slightly higher (20–60 %) exposure in subjects with CKD compared with subjects with normal renal function, the steady-state AUC and C_{max} values showed a large overlap and were not affected by the degree of CKD (Table 1). Almost similar results were obtained after one single dose and after multiple doses for 7 days when comparing results in patients with CKD and those in normal subjects.

The same study compared linagliptin pharmacokinetics in 10 T2DM patients with severe CKD (CL_{CR} ≤30 mL/min) and in 11 T2DM patients with normal renal function (CL_{CR} >80 mL/min) again in two conditions: after a single dose of 5 mg linagliptin and after a multiple-dose regimen of linagliptin 5 mg once daily for 7 days [41]. In T2DM subjects with severe CKD, exposure after a single dose was only slightly increased compared with that in T2DM patients with normal renal function: 155 versus 127 nmol·h/L for AUC from 0 to 24 h ($AUC_{0–24}$) and 12.2 versus 10.0 nmol/L for C_{max}. Similarly, steady-state exposure was only modestly increased: the geometric mean ratio (GMR) was 1.42 for AUC during a dosage interval at steady state ($AUC_{\tau,ss}$; 90 % CI 1.10–1.82) and 1.36 for C_{max} at steady state ($C_{max,ss}$; 90 % CI 0.97–1.90) when comparing patients with severe CKD and patients with normal renal function. Overall, only a weak correlation was found between steady-state exposure and renal function across all patient groups, indicating that for the majority of patients, regardless of renal status, linagliptin exposure remained within the same range [41].

The minor, almost negligible, effect of CKD on linagliptin pharmacokinetics has been confirmed in post hoc analyses of the trough plasma levels of linagliptin in the global phase 3 programme investigating linagliptin 5 mg once daily for 24–52 weeks in patients with T2DM and various degrees of CKD [77]. Data were pooled from three randomized studies from the global phase 3 programme of linagliptin (5 mg daily in each) in patients with T2DM. Linagliptin plasma concentrations were available for 969 patients who were determined by eGFR to have normal renal function ($n = 438$), mild CKD ($n = 429$), moderate CKD ($n = 44$) or severe CKD ($n = 58$). In patients with normal renal function, the geometric mean linagliptin trough concentration (coefficient of variation) was 5.93 nmol/L (56.3 %); in patients with mild, moderate or severe renal impairment, geometric mean concentrations were 6.07 nmol/L (62.9 %), 7.34 nmol/L (58.6 %) and 8.13 nmol/L (49.8 %), respectively. Thus, in patients with T2DM, CKD had a minor effect on linagliptin exposure. Therefore, neither dose adjustment of linagliptin nor drug-related monitoring of eGFR is necessary for patients with CKD [77].

4.5.2 Clinical Use

The efficacy and safety of linagliptin in comparison with other antidiabetic drugs in T2DM patients with renal and cardiovascular risk factors have been recently reviewed as well as an outlook on the perspective for linagliptin in this patient population in the future [76].

A pooled analysis of three clinical trials evaluated the effect of renal function on the efficacy and safety of linagliptin. Data were available for 2,141 patients with T2DM who were grouped by renal function as normal ($n = 1{,}212$), mild CKD ($n = 838$) or moderate CKD ($n = 93$). Linagliptin showed consistent placebo-corrected adjusted mean HbA_{1c} changes after 24 weeks across all three groups: normal renal function (−0.63 %), mild CKD (−0.67 %) and moderate CKD (−0.53 %), with no significant between-group difference. Linagliptin was generally well tolerated, with an incidence rate of adverse events with linagliptin similar to placebo, even in patients with mild to moderate CKD [78].

A phase 3 trial evaluated the efficacy and safety of linagliptin in patients with T2DM and severe CKD (GFR <30 mL/min/1.73 m^2) [79]. Patients were treated with either linagliptin 5 mg once daily or placebo. Linagliptin induced significantly greater HbA_{1c} reductions at week 12 compared with baseline in the full analysis set (−0.8 versus −0.2 % with placebo) and in the subgroup of poorly controlled patients (baseline HbA_{1c} ≥9 %) (−1.5 versus −0.3 %). Hypoglycaemia occurred more frequently in linagliptin-treated patients than in placebo-treated patients, an observation that may be explained by unchanged doses of insulin and/or sulphonylurea background therapy. Other adverse event rates were similar for linagliptin and placebo. The findings were confirmed in a 1-year, randomized, double-blind, placebo-controlled study demonstrating the favourable safety and efficacy profile of linagliptin in patients with T2DM and severe CKD [80].

Finally, a pooled analysis of four completed studies identified 217 subjects with T2DM and prevalent albuminuria (defined as a urinary albumin to creatinine ratio of 30–3,000 mg/g creatinine) while receiving stable doses of inhibitors of the renin–angiotensin system. Participants were randomized to either linagliptin 5 mg/day or placebo. Linagliptin led to a significant reduction in albuminuria in patients with T2DM and renal dysfunction. This observation was independent of changes in glucose level or systolic blood pressure [81]. These results should trigger further research to prospectively investigate the renal effects of linagliptin.

4.6 Gemigliptin

4.6.1 Pharmacokinetics

Gemigliptin is a new, potent, selective and long-acting DPP-4 inhibitor, already commercialized in Korea under the trade name Zemiglo® [82], but not available in Europe or in the USA yet. In a single-dose study (25, 50, 100, 200, 400 or 600 mg of gemigliptin) in healthy male Korean subjects, the mean fraction of unchanged drug excreted in urine ranged from 0.21 to 0.34 and mean CL_R was 15.5–23.6 L/h [83]. These data were confirmed in a multiple-dose study (200, 400 or 600 mg of gemigliptin once daily for 10 days). The mean fraction of unchanged drug excreted in urine was independent of dose and in the range of 0.40–0.48. CL_R of gemigliptin ranged from 18.6 to 21.9 L/h or 310 to 365 mL/min at steady state [84].

In a study evaluating the effects of CKD and haemodialysis on the pharmacokinetics of gemigliptin (single dose of 100 mg) [85], patients with mild, moderate and severe CKD and ESRD showed 1.20, 2.04, 1.50 and 1.66-fold (1.69 for haemodialysed patients) increases of AUC_∞, respectively, and 1.10, 1.49, 1.22 and 1.21-fold (1.25 for haemodialysed patients) increases of C_{max} of gemigliptin, respectively (Table 1). The pharmacokinetics of gemigliptin were comparable between haemodialysis and non-haemodialysis periods in ESRD patients and less than 4 % of the dose was removed by 4 h of haemodialysis. Thus, CKD appeared to have a modest effect on the gemigliptin disposition and so no dose adjustment in patients with CKD is proposed on the basis of exposure–response relationship. Impact of haemodialysis on the removal of gemigliptin was negligible [85].

4.6.2 Clinical Use

Because gemigliptin is not available yet in Europe and in the USA, the clinical experience with this compound, especially in patients with CKD, is limited.

5 GLP-1 Receptor Agonists

When oral therapy is not sufficient to control blood glucose, injectable agents may be used. Besides insulin therapy, GLP-1 receptor agonists offer new opportunities for the management of T2DM [5] and several once- or twice-daily agents are already available (exenatide, liraglutide, lixisenatide) [86]. A long-acting release (LAR) formulation of exenatide has been commercialized permitting a once-weekly injection [87] and other once-weekly GLP-1 receptor agonists are in late phase of development (albiglutide, dulaglutide, semaglutide) [88]. However, because most of these GLP-1 receptor agonists are at least partially eliminated by the kidneys, some limitations have been pointed out in presence of CKD [27]. Based on the current evidence, exenatide is eliminated by renal mechanisms [89] and should not be given in patients with severe CKD or ESRD [90]. Liraglutide is not eliminated by renal or hepatic mechanisms, but it should be used with caution since there are only limited data in patients with CKD [91].

5.1 Exenatide

5.1.1 Pharmacokinetics

The pharmacokinetics of a single exenatide dose were evaluated in patients with CKD. Exenatide (5 or 10 μg) was injected subcutaneously in 31 subjects (only one with T2DM) stratified by renal function: normal (CL_{CR} >80 mL/min), mild CKD (51–80 mL/min), moderate CKD (31–50 mL/min) or ESRD requiring haemodialysis [92]. Pharmacokinetic data were combined with four previous single-dose studies in patients with T2DM to explore the relationship of exenatide clearance (CL/F) and CL_{CR}. Mean $t_{½}$ for healthy, mild CKD, moderate CKD and ESRD groups were 1.5, 2.1, 3.2 and 6.0 h, respectively (Table 2). After combining data from multiple studies, least squares geometric means for CL/F in subjects with normal renal function, mild CKD, moderate CKD and ESRD were 8.14, 5.19, 7.11 and 1.3 L/h, respectively. Thereby, exposure (AUC) to exenatide was markedly increased in patients with ESRD (Table 2).

Exenatide LAR has been developed for once-weekly subcutaneous injection [87]. The pharmacokinetics of exenatide LAR 2 mg have been evaluated in 56 patients with mild CKD (CL_{CR} 50–80 mL/min) and in 10 patients with moderate CKD (CL_{CR} 30–50 mL/min; median value 44 mL/min) as compared with 84 patients with normal CL_{CR} (unpublished data) (FDA Assessment Report) [93]. Exenatide LAR has not been studied in subjects with severe CKD (CL_{CR} <30 mL/min). Baseline CL_{CR} was determined to be the most significant predictor of steady-state concentration of exenatide following once-weekly dosing. There was a 24 % increase in the observed average steady-state concentrations in patients with mild renal impairment and 53 % in those with moderate CKD as compared with patients with normal renal function. The maximum predicted increase in steady-state concentrations for patients with CL_{CR} 30 mL/min is 2-fold. Thus caution is recommended when using exenatide LAR in patients with moderate CKD and the drug should not be used in patients with severe CKD.

5.1.2 Clinical Use

Exenatide was generally well tolerated in the mild and moderate CKD groups, but not in subjects with ESRD because of nausea and vomiting. Since tolerability and pharmacokinetic changes were considered clinically acceptable in patients with mild to moderate CKD, it would be appropriate to administer exenatide to these patients without dosage adjustment. However, poor tolerability and significant changes in pharmacokinetics make the currently available therapeutic doses (5 and 10 μg) unsuitable in severe CKD or ESRD [92].

The clinical experience of exenatide twice-daily formulation [90] or exenatide once-weekly formulation [87] is rather limited in T2DM patients with CKD. In a large retrospective observational study, there were no significant differences in change in kidney function (eGFR) or albuminuria (urinary albumin to creatinine ratio) at 1 year in patients treated with exenatide twice daily compared with insulin glargine as administered in routine practice [94].

5.2 Liraglutide

5.2.1 Pharmacokinetics

Liraglutide is a GLP-1 receptor agonist with a rather long half-life (11–15 h) allowing a once-daily subcutaneous injection for the management of T2DM [91]. To investigate whether dose adjustment of the once-daily human GLP-1 analogue liraglutide is required in patients with varying stages of CKD, 30 subjects were given a single dose of liraglutide 0.75 mg subcutaneously [95]. No clear trend for change in pharmacokinetics was evident across groups with increasing renal dysfunction. The regression analysis of log(AUC) for subjects with normal renal function and mild-to-severe CKD showed no significant effect of decreasing CL_{CR} on the pharmacokinetics of liraglutide (Table 2). Thus, overall, none of the renal impairment groups presented with higher mean liraglutide exposure than the healthy reference group. In contrast, an unexplained minor lowering of liraglutide exposure with decreasing CL_{CR} cannot be ruled out. Liraglutide $t_{½}$ was not found to be increased and clearance was not found to be decreased in subjects with CKD. Thus, these pharmacokinetic results support the observation that the kidneys are not a major site for elimination and degradation of liraglutide. Because renal dysfunction was not found to increase exposure of liraglutide, T2DM patients with CKD should use standard treatment regimens of liraglutide. There is, however, currently limited experience with liraglutide in patients beyond mild-stage CKD [95].

5.2.2 Clinical Use

In the acute pharmacokinetic study, the degree of CKD did not appear to be associated with an increased risk of adverse events [95]. To determine the effect of mild CKD on the efficacy and safety of liraglutide in patients with T2DM, the six LEAD (Liraglutide Effect and Action in Diabetes) clinical trials were examined in a meta-analysis focusing on data from patients with normal renal function (CL_{CR} >89 mL/min), mild CKD (60–89 mL/min) and moderate or severe CKD (<60 mL/min). The population contained patients administered once-daily liraglutide (1.2 or 1.8 mg) or placebo as either monotherapy or in

Table 2 Key pharmacokinetic parameters of glucagon-like peptide-1 (GLP-1) receptor agonists in subjects with various degrees of chronic kidney disease (CKD; according to the level of creatinine clearance) compared with subjects with normal renal function (no CKD). Results are expressed as mean data ± standard deviation ([a]) or mean data with [% coefficient of variation] ([b]), except for time to reach maximum concentration (t_{max}; median, range)

Drug and parameter	Dosing reference	No CKD	Mild CKD	Moderate CKD	Severe CKD	Haemodialysis
Exenatide	Single-dose	$N = 8$	$N = 8$	$N = 5$		$N = 8$
AUC_{∞} (pg·h/mL)	10 μg (normal, mild CKD),	2,930 [31.4][b]	2,080 [17.4][b]	1,150 [15.2][b]	NA	5,380 [42.2][b]
GMR (90 % CI)	5 or 10 μg (moderate CKD),		0.81 (0.66–0.98)	0.97 (0.77–1.21)	NA	3.37 (2.80–4.06)
C_{max} (pg/mL)	5 μg (haemodialysis)	821 [61.0][b]	470 [24.6][b]	202 [19.9][b]	NA	601 [69.4][b]
GMR (90 % CI)	Linnebjerg et al. [92]		0.68 (0.49–0.93)	0.65 (0.45–0.94)	NA	1.38 (1.01–1.88)
t_{max} (h; median, range)		2.0 (1.0–3.0)	2.0 (0.5–3.0)	2.5 (1.0–3.0)	NA	2.0 (1.0–4.0)
$t_{½}$ (h; mean, range)		1.5 (0.9–2.0)	2.1 (1.6–3.4)	3.2 (1.8–7.0)	NA	6.0 (4.3–7.6)
CL/F (L/h)		3.4 [31.4][b]	4.8 [17.4][b]	4.4 [14.2][b]	NA	0.9 [42.2][b]
Liraglutide	Single-dose	$N = 6$	$N = 6$	$N = 7$	$N = 5$	$N = 6$
AUC_{∞} (nmol·h/L)	0.75 mg	274.3 ± 71.4[a]	219.8 ± 76.6[a]	256.7 ± 63.2[a]	273.6 ± 61.4[a]	265.4 ± 104.2[a]
GMR (90 % CI)	Jacobsen et al. [95]		0.67 (0.54–0.85)	0.86 (0.70–1.07)	0.73 (0.57–0.94)	0.74 (0.56–0.97)
C_{max} (nmol/L)		9.25 ± 2.47[a]	7.87 ± 2.79[a]	9.17 ± 2.45[a]	9.17 ± 1.96[a]	10.48 ± 4.87[a]
GMR (90 % CI)			0.75 (0.57–0.98)	0.96 (0.74–1.23)	0.77 (0.57–1.03)	0.92 (0.67–1.27)
t_{max} (h; median, range)		12.50 (11.5–21.0)	12.00 (9.5–16.0)	12.50 (11.0–16.0)	11.00 (10.0–14.0)	10.25 (6.0–12.5)
$t_{½}$ (h)		14.25 ± 3.21[a]	11.90 ± 1.40[a]	11.90 ± 1.01[a]	11.88 ± 1.80[a]	11.13 ± 0.91[a]
CL/F (L/h)		0.79 ± 0.29[a]	1.00 ± 0.32[a]	0.82 ± 0.22[a]	0.76 ± 0.18[a]	0.86 ± 0.33[a]
Lixisenatide	Single-dose	$N = 8$	$N = 8$	$N = 8$	$N = 8$	
AUC_{last} (pg·h/mL)	5 μg	210 ± 90[a]	211 ± 104[a]	274 ± 116[a]	346 ± 116[a]	NA
GMR (90 % CI)	Liu et al. [100]		0.94 (0.62–1.41)	1.28 (0.85–1.93)	1.67 (1.12–2.51)	NA
C_{max} (pg/mL)		54 ± 28[a]	50 ± 19[a]	54 ± 27[a]	64 ± 15[a]	NA
GMR (90 % CI)			0.98 (0.68–1.41)	0.99 (0.69–1.43)	1.29 (0.90–1.86)	NA
t_{max} (h; median, range)		2.3 (0.5–3.0)	2.3 (0.5–3.0)	2.3 (1.5–3.5)	1.8 (1.5–3.5)	NA
$t_{½}$ (h)		2.60 ± 1.00[a]	2.40 ± 1.20[a]	2.60 ± 0.80[a]	2.90 ± 1.20[a]	NA
CL/F (L/h)		20.0 ± 6.2[a]	19.0 ± 6.5[a]	16.0 ± 5.7[a]	14.0 ± 5.4[a]	NA
Albiglutide	Single-dose	$N = 10$		$N = 11$	$N = 10$	$N = 10$
AUC_{∞} (ng·h/mL)	30 mg	297,939 [27][b]	NA	493,649 [26][b]	561,982 [65][b]	445,271 [74][b]
GMR (90 % CI)	Young et al. [103]		NA	1.32 (0.96–1.80)	1.39 (1.03–1.89)	0.99 (0.63–1.57)
C_{max} (ng/mL)		887.1 [33][b]	NA	1,395.5 [44][b]	1,456.9 [71][b]	1,524.7 [76][b]
GMR (90 % CI)			NA	1.21 (0.90–1.63)	1.23 (0.91–1.67)	1.11 (0.72–1.73)
t_{max} (h; median, range)		96 (48–216)	NA	96 (48–218)	96 (24–221)	88 (33–146)
$t_{½}$ (h)		127.5 [16][b]	NA	142.4 [23][b]	145.2 [26][b]	141.3 [26][b]
CL/F (mL/h)		100.7 [27][b]	NA	60.8 [26][b]	53.4 [65][b]	67.4 [74][b]

AUC area under plasma concentration–time curve, AUC_{0-24} AUC from 0 to 24 h, AUC_{last} AUC from time zero to time of last measurable concentration, AUC_{∞} AUC from time zero to infinity, *CI* confidence interval, *CL/F* total apparent plasma clearance, C_{max} maximum plasma concentration, *GMR* geometric mean between renal impairment and normal kidney function, *NA* not available, $t_{½}$ terminal plasma half-life, t_{max} time to reach maximum concentration

combination with oral antidiabetic drugs for 26 weeks. Mild CKD did not affect the estimated treatment differences in HbA_{1c}, body weight and systolic blood pressure. Liraglutide treatment was safe and well tolerated in patients with mild CKD, as there were no significant differences in changes in rates of renal injury, minor hypoglycaemia or nausea versus placebo. Nevertheless, a trend towards increased nausea was observed in patients with moderate or severe CKD receiving liraglutide although the number of patients in this treatment group was too low to determine statistical significance. The conclusion was that mild CKD had no effect on the efficacy and safety of liraglutide [96]. There is, however, currently limited experience with liraglutide in patients beyond mild-stage CKD [95].

A pilot Japanese study investigated the effect of liraglutide on proteinuria and GFR decline in T2DM patients with overt diabetic nephropathy, who had already been treated with blockade of the renin–angiotensin system under dietary sodium restriction. The administration of liraglutide significantly reduced albuminuria and also substantially diminished the rate of decline in eGFR, suggesting that the GLP-1 receptor agonist may attenuate the progression of diabetic nephropathy in T2DM [97]. These preliminary results require further confirmation.

5.3 Lixisenatide

5.3.1 Pharmacokinetics

Lixisenatide is a new once-daily agonist with a high affinity for the GLP-1 receptor and particularly strong effects on postprandial plasma glucose levels [98, 99]. The effects of CKD on the pharmacokinetics of lixisenatide were investigated in a single-centre, single-dose (5 μg given subcutaneously), open-label, nonrandomized, parallel-group study recruiting patients (8 in each group; 72-h blood sampling period) with normal renal function, mild CKD, moderate CKD and severe CKD (but not requiring haemodialysis) (data only published in abstract form) [100]. No significant differences in AUC from time zero to time of last measurable concentration (AUC_{last}) or C_{max} were observed for subjects with mild CKD or moderate CKD versus the reference normal function group (Table 2). In subjects with severe renal impairment, there was a significant increase in AUC_{last} (GMR 1.67; 95 % CI 1.12–2.51), but not in C_{max} (GMR 1.29; 95 % CI 0.90–1.86) (Table 2). Thus, mild or moderate CKD does not appear to influence the pharmacokinetics of lixisenatide, but drug exposure may increase in patients with severe CKD [100].

5.3.2 Clinical Use

A post hoc assessment evaluated the efficacy and safety of lixisenatide in patients with T2DM and renal impairment. Patients from nine GetGoal trials were categorized by baseline CL_{CR} levels as having normal renal function, mild CKD or moderate CKD [101]. Meta-analyses of placebo-adjusted mean differences between baseline renal categories showed nonsignificant differences regarding reductions in HbA_{1c}, 2 h postprandial plasma glucose and fasting plasma glucose levels. Thus, a uniform effect of lixisenatide was observed across renal categories. Placebo-corrected incidence of gastrointestinal averse events (mainly nausea and vomiting) was slightly higher in mild (27.8 %) and moderate (28.5 %) CKD groups compared with patients with normal renal function (19.4 %) [101].

No dose adjustment is required for T2DM patients with mild CKD. There is limited therapeutic experience in patients with moderate CKD and lixisenatide should be used with caution in this population. There is no therapeutic experience in patients with severe CKD or ESRD and, therefore, it is not recommended to use lixisenatide in these populations [98].

5.4 Albiglutide

5.4.1 Pharmacokinetics

Albiglutide (Eperzan® [EU]; Tanzeum™ [USA]) is a new once-weekly GLP-1 receptor agonist that has been developed by GlaxoSmithKline for the treatment of T2DM [102]. The pharmacokinetics of albiglutide were assessed from a single-dose (30 mg), nonrandomized, open-label study in 41 subjects with normal and varying degrees of CKD, including haemodialysis [103]. Single-dose pharmacokinetics showed AUCs of 1.32 (90 % CI 0.96–1.80), 1.39 (1.03–1.89) and 0.99 (0.63–1.57) for the moderate CKD, severe CKD and haemodialysis groups, respectively, relative to the normal group (Table 2).

Furthermore, the pharmacokinetics of once-weekly albiglutide were assessed in a pooled analysis of four phase 3, randomized, double-blind (one open-label), active or placebo-controlled, multiple-dose studies [103]. The pooled analysis of the latter four studies ($n = 1{,}113$) was part of the population pharmacokinetic analysis, which included subjects with normal renal function and varying degrees of CKD (mild, moderate, severe) treated with albiglutide (30–50 mg) to primary end points of 26–52 weeks. Results indicate that modest increases in plasma concentrations of albiglutide were observed with the severity of CKD.

5.4.2 Clinical Use

In addition to pharmacokinetic analysis, both efficacy and safety of once-weekly albiglutide were assessed in this pooled analysis of four phase 3, active or placebo-controlled, multiple-dose studies [103]. There was a trend for a more potent glucose-lowering effect as the eGFR decreased. The group with severe CKD had a higher frequency of gastrointestinal events (e.g. diarrhoea, constipation, nausea and vomiting) and hypoglycaemic events (with background sulphonylurea use) compared with patients with mild or moderate CKD.

Thus, the pharmacokinetics, efficacy and safety data indicate that albiglutide has a favourable benefit to risk ratio in patients with T2DM and varying degrees of CKD, and the need for a dose adjustment is not suggested. However, experience in patients with more severe CKD is very limited, so the recommendation is to use albiglutide carefully in this population [103].

6 Discussion

Incretin-based therapies are increasingly used for the treatment of T2DM, essentially because of good glucose-lowering activity without inducing hypoglycaemia or weight gain [14]. DPP-4 inhibitors [15] and GLP-1 receptor agonists [86] are positioned, among other pharmacological options, as second-line treatment after failure of metformin monotherapy or later on in triple therapy within various combinations [5]. DPP-4 inhibitors have the advantages to be administered orally, to have an excellent tolerance profile and to be less expensive, but they are less potent and weight-neutral only compared with GLP-1 receptor agonists. Alternatively, GLP-1 receptor agonists offer a greater HbA_{1c} reduction and significant weight loss, but they must be injected subcutaneously, may be associated with nausea and vomiting (especially during the first weeks after initiation of therapy) and are more expensive. Consequently, the choice between a DPP-4 inhibitor and a GLP-1 receptor agonist should be made on an individual basis according to physician objectives and patient preference [5]. One of the criteria to be taken into account may be kidney function because of some restrictions in clinical use of various incretin-based medications in presence of some degree of CKD, especially for GLP-1 receptor agonists (Tables 3, 4) [27].

Results from dedicated pharmacokinetic studies in subjects with various degrees of CKD suggest that the daily doses of the first four DPP-4 inhibitors commercialized (sitagliptin, vildagliptin, saxagliptin, alogliptin), which are characterized by predominantly renal excretion, should be adjusted according to eGFR to reach almost similar plasma levels (Fig. 1) [21]. Several studies have demonstrated that the glucose-lowering efficacy is maintained while there is a good safety profile when reduced doses of these gliptins are used in patients with mild to severe CKD [43, 55, 56, 67]. Not surprisingly, however, in everyday life, sitagliptin has been shown to be frequently administered at inappropriate doses in patients with CKD [104]. Furthermore, the coexistence of two formulae to estimate renal function—the Cockcroft–Gault formula and the Modification of Diet in Renal Disease (MDRD) formula—may lead to some discrepancies in dosing adjustment as recently illustrated with the use of sitagliptin in clinical practice [105]. In contrast, because of its predominantly hepatobiliary excretion, linagliptin does not require any dose adjustment in the case of CKD and can be safely used in patients with various degrees of CKD (Tables 3, 4) [78, 79].

Because DPP-4 inhibitors are most often used in association with metformin, the first-line drug choice for the management of T2DM [106], several fixed-dose combinations (FDCs) are currently available [107]: sitagliptin–metformin [108], vildagliptin–metformin [52, 109], saxagliptin–metformin [110], linaglipin–metformin [111] and alogliptin–metformin. Such FDCs may only be prescribed when both compounds are not contraindicated because of the presence of CKD and appropriate adjustments of individual doses may be required. There is some controversy about the use of metformin in T2DM patients with CKD, especially the level of eGFR beyond which metformin is contraindicated [5, 112]. The recent scientific literature suggests that reconsidering the contraindications of metformin is urgently needed in order to avoid physicians prescribing the most popular glucose-lowering therapy in daily clinical practice outside the official recommendations [113]. Nevertheless, caution should be recommended when using a gliptin–metformin FDC in patients with CKD [114].

GLP-1 receptor agonists may represent an alternative to insulin therapy for patients not successfully treated with oral antidiabetic agents [5, 115]. In the case of CKD, insulin may be used without restriction. Because the hormone is largely clearly by the kidneys, caution is recommended to the clinician as a reduction of daily insulin dose may be necessary to avoid hypoglycaemia. However, the clinical experience of using insulin in CKD patients is considerable, especially because basic oral glucose-lowering agents such as metformin and many sulphonylureas are classically contraindicated in presence of moderate to severe CKD [18]. Concerning GLP-1 receptor agonists, the pharmacokinetic data appear reassuring (Fig. 2), but the clinical experience in patients with CKD is still limited [20]. No dosage adjustment of exenatide is required for patients with mild to moderate CKD [90]. Indeed, the recommended starting dose of 5 μg twice daily was well

Table 3 Clinical practice recommendations regarding the use of dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists in patients with type 2 diabetes mellitus with various degrees of chronic kidney disease (CKD) according to the glomerular filtration rate (GFR)

Incretin-based therapies	Exposure (AUC) in patients with CKD	Use according to GFR (mL/min)	Use in patients with ESRD and haemodialysis
DPP-4 inhibitors			
Sitagliptin	Increased	≥50: yes 30–50: half dose <30: quarter dose	Caution
Vildagliptin	Increased	≥50: yes <50: half dose	Caution
Saxagliptin	Increased (+ active metabolite)	≥50: yes <50: half dose <30: caution	No
Alogliptin	Increased	≥50: yes <50: reduced dose	Caution
Linagliptin	No change	Yes (without dose adjustment)	Possibly yes (no data)
Gemigliptin[a]	Slightly increased	Probably yes	Possibly yes (no data)
GLP-1 receptor agonists			
Exenatide	Increased	≥60: yes 30–60: caution <30: no	No
Exenatide LAR	Increased	≥60: yes 30–60: caution <30: no	No
Liraglutide	No change (or slightly decreased)	≥50: yes <50: no	No
Lixisenatide	Slightly increased	≥50: yes 30–50: caution <30: no	No

AUC area under concentration–time curve, *ESRD* end-stage renal disease, *LAR* long-acting release

[a] Limited experience because not available in Europe or in the USA

Table 4 Dose adjustments recommended when using incretin-based therapies in patients with various stages of chronic kidney disease (CKD) based on previous pharmacokinetic studies

CKD Stage	Mild 1–2	Moderate 3	Severe 4	ESRD 5
CL_{CR} (mL/min)	≥50	≥30 to <50	<30	Haemodialysis
Sitagliptin	100 mg/day	50 mg/day	25 mg/day	25 mg/day
Vildagliptin	2 × 50 mg/day	1 × 50 mg/day	1 × 50 mg/day	1 × 50 mg/day
Saxagliptin	5 mg/day	2.5 mg/day	2.5 mg/day	NR
Alogliptin	25 mg/day	12.5 mg/day	6.25 mg/day	6.25 mg/day
Gemigliptin[a]	50 mg/day	50 mg/day	50 mg/day	50 mg/day
Linagliptin	5 mg/day	5 mg/day	5 mg/day	5 mg/day
Exenatide	2 × 10 μg/day	2 × 10 μg/day	NR	NR
Exenatide LAR	2 mg/week	2 mg/week	NR	NR
Liraglutide	1.2–1.8 mg/day	NR	NR	NR
Lixisenatide	1 × 20 μg/day	1 × 20 μg/day	NR	NR

CL_{CR} creatinine clearance, *ESRD* end-stage renal disease, *LAR* long-acting release, *NR* not recommended

[a] Limited experience because not available in Europe or in the USA

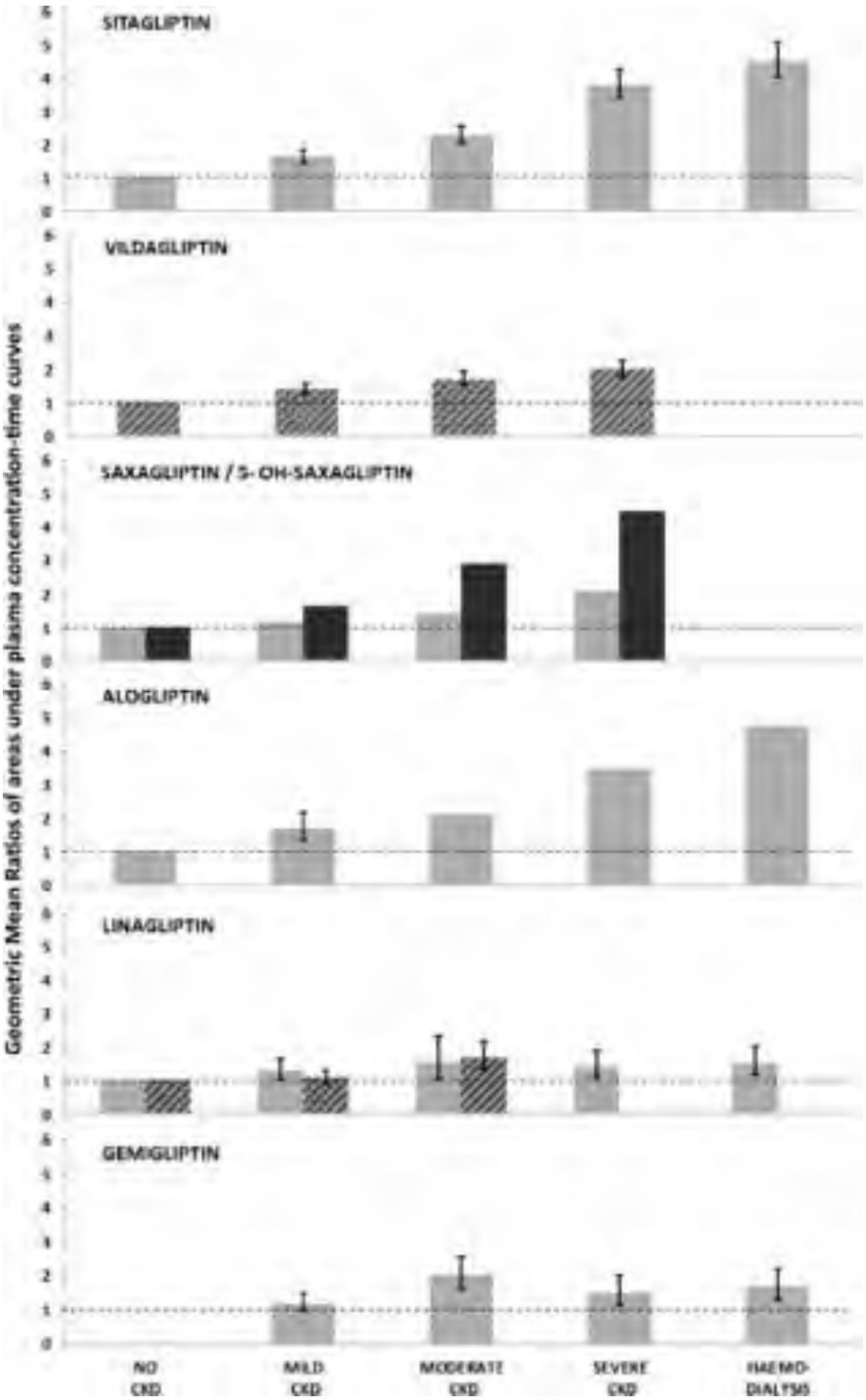

Fig. 1 Comparison of geometric mean ratios (with 90 % confidence intervals when available) of areas under plasma concentration–time curves (total exposure) for sitagliptin, vildagliptin, saxagliptin and its active metabolite 5-hydroxy (OH)-saxagliptin, alogliptin, linagliptin and gemigliptin in patients with mild (creatinine clearance [CL_{CR}] 51–80 mL/min), moderate (CL_{CR} 31–50 mL/min), severe (CL_{CR} ≤30 mL/min) chronic kidney disease (CKD) and end-stage renal disease treated by haemodialysis compared with patients with normal kidney function (no CKD; CL_{CR} >80 mL/min). *Grey bars* correspond to data after a single dose while *hatched bars* correspond to data after multiple doses. *Black bars* correspond to 5-OH-saxagliptin

tolerated in this population and any subsequent increase in dosage would be based on the patient's individual tolerance and glycaemic response. However, as mean exenatide clearance was significantly reduced by about 70 % and a single 5 μg dose of exenatide was not well tolerated in patients with ESRD, exenatide may not be suitable for use in patients with severe CKD (CL_{CR} <30 mL/min) or ESRD, at least at the current therapeutic dose [92]. As far as liraglutide is concerned, the available data indicated that the pharmacokinetics of liraglutide are essentially independent of renal function [95]. However, lower exposure with CKD cannot be excluded based on the available data [95]. No safety concerns were raised in the available pharmacokinetic and clinical studies. In particular, the

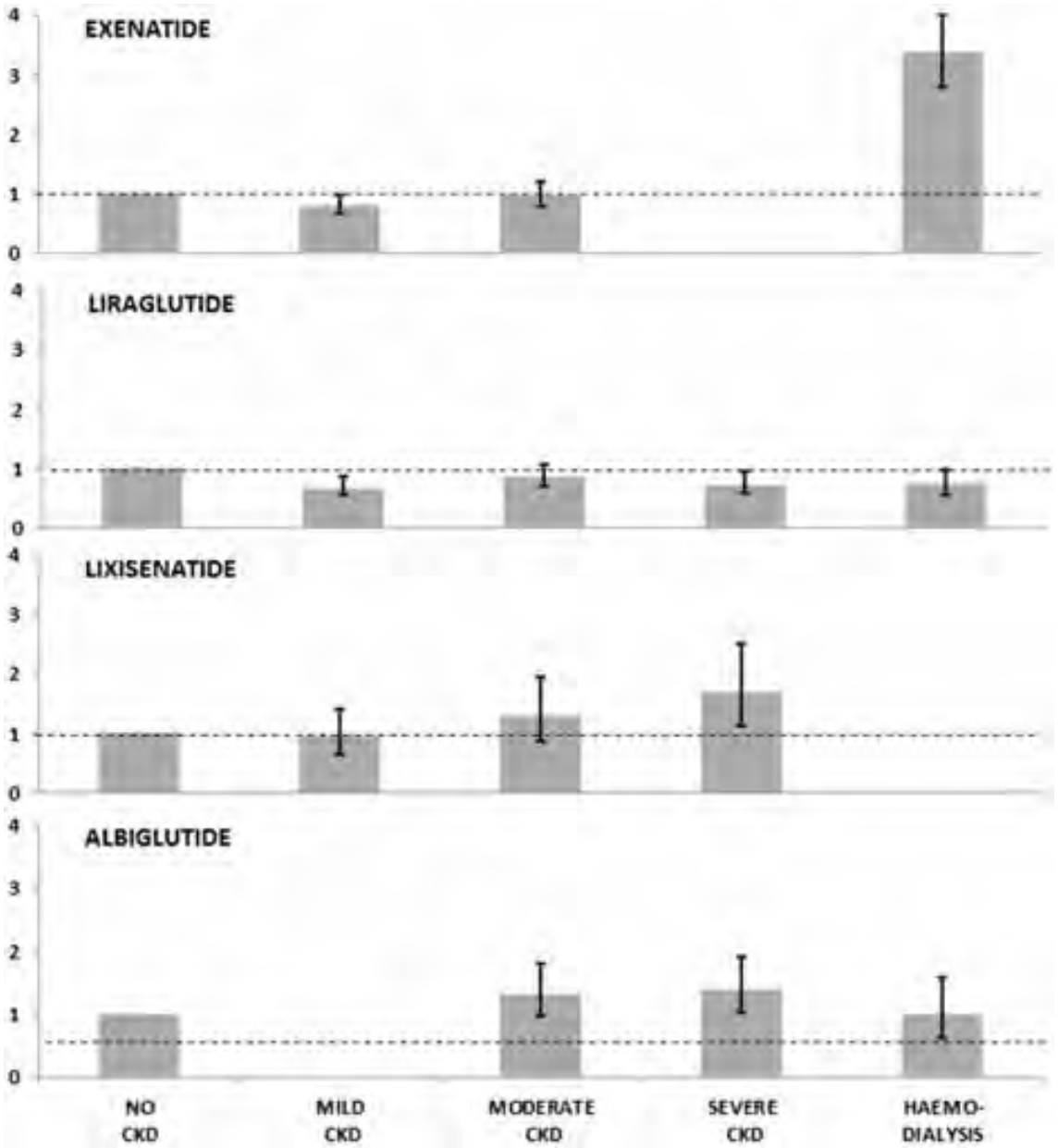

Fig. 2 Comparison of geometric mean ratios (with 90 % confidence intervals) of areas under plasma concentration–time curves for exenatide, liraglutide, lixisenatide and albiglutide in patients with mild (creatinine clearance [CL_{CR}] 51–80 mL/min), moderate (CL_{CR} 31–50 mL/min), severe (CL_{CR} ≤30 mL/min) chronic kidney disease (CKD) and end-stage renal disease treated by haemodialysis compared with patients with normal kidney function (no CKD; CL_{CR} >80 mL/min)

degree of CKD of subjects did not appear to be associated with an increased risk of adverse events, except perhaps a trend for higher incidence of nausea [96]. Therefore, one can expect that T2DM patients with CKD will be able to use standard treatment regiments for liraglutide without dose adjustments [91]. Nevertheless, there is currently limited experience with liraglutide in patients beyond mild-stage CKD and thus caution is required (Tables 2, 3) [95].

Published case reports have documented the relationship between exenatide [116–121] or liraglutide [121–123] use and acute kidney injury in patients with T2DM. Both acute interstitial nephritis and acute tubular necrosis may account for GLP-1 receptor agonist-related acute renal failure [121]. One of the proposed explanations was the occurrence of gastrointestinal side effects with recurrent vomiting leading to dehydration and secondary acute kidney disease. Although prerenal acute kidney injury appears to be exceptional with the use of GLP-1 receptor agonists, physicians should be aware of this adverse event and patients should also be educated about the need to quickly report unusual or prolonged gastrointestinal symptoms. However, a retrospective cohort study of a large medical

and pharmacy claims database revealed an increased incidence of acute renal failure in diabetic versus nondiabetic patients but no association between use of exenatide and acute renal failure [124].

Finally, some experimental data suggested that incretin-based therapies may exert positive renal effects which could exert some protection against the development or worsening of diabetic nephropathy [24–26]. Clinical studies supporting GLP-1-mediated renal protection exist, but they are few and with limitations [97]. In the large prospective SAVOR-TIMI 53 cardiovascular outcomes trial, microalbuminuria was positively influenced by saxagliptin as compared with placebo. However, hard renal end points were similar in the saxagliptin group and placebo group, possibly because of a too short follow-up period [68]. Therefore, the renoprotective potential of GLP-1 therapy needs to be thoroughly investigated in humans.

7 Conclusion

The increasing prevalence of T2DM and CKD, especially among elderly people, requires regular monitoring of renal function and appropriate selection and dosing of glucose-lowering agents according to GFR. A careful benefit/risk balance assessment should be performed in these more fragile diabetic patients. While carefully conducted pharmacokinetic studies are lacking with most of the ancient commonly prescribed oral glucose-lowering agents, nice pharmacokinetic studies have been recently published with almost all incretin-based medications. The pharmacokinetics of DPP-4 inhibitors (except linagliptin) and GLP-1 receptor agonists (especially exenatide) are modified by CKD, which may require appropriate dose reductions. The clinical experience with DPP-4 inhibitors in T2DM patients with CKD is already quite substantial and the efficacy–safety profile has been demonstrated in many controlled studies using appropriate dose adjustment according to GFR decline when requested. Of interest, patients with CKD represent a specific subpopulation that may take advantage of using a DPP-4 inhibitor instead of a sulphonylurea in order to reduce the potential risk of hypoglycaemia. The clinical experience with GLP-1 receptor agonists is more limited and so the use of exenatide, liraglutide or lixisenatide should be cautious in patients with CKD until further studies are available demonstrating the efficacy and safety of these medications in patients with moderate to severe CKD.

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